Remarks

In response to the Office Action mailed 12 December 2007 the applicant herein submits the following amendments and remarks.

The applicant provides the following submissions with this communication: 1) applicant's facsimile cover page; 2) Transmittal Form (PTO/SB/21), 3) Certificate of Transmission (PTO/SB/97); 4) Petition for 3 Month Extension of Time under 37 C.F.R. §1.136(a) (PTO/SB/22); and 5) the applicant's substantive Amendment and Response (40) pages).

The Office Action set a three-month Shortened Statutory Period extendable until 12 March 2008 under 37 C.F.R. §1.136(a) for submission of a responsive communication. Applicant's response is timely in view of the three (30 month Petition for Extension and payment of extension fee pursuant to 37 C.F.R. §1.17(a)(3). The applicant authorizes the Commissioner to charge, or credit any overpayment, associated/necessary with this communication to U.S.P.T.O. Deposit Account No.: 50-0244.

Claims 18-36, 46, 48-51, 56 and 57 are currently pending. The applicant has amended claims 18, 22, 29, 33, 35, and 48 in order to advance prosecution and his business interests without acquiescing to the Examiner's arguments and while reserving the right to prosecute claims directed to any canceled or amended subject matter in the future. The claim amendments are fully supported by the specification as originally filed and do not add new matter. Furthermore, the applicant has canceled claims 56 and 57, without prejudice, for like reasons and while reserving the right to prosecute the original, or similar, claims in the future.

In view of the applicant's most recent paper, his 20 September 2007 Amendment and Response, the Examiner withdrew the following rejections made in the 20 March 2007 Final Office Action:

1. The rejection of claim 19 under 35 U.S.C. §112, ¶ 2, as being indefinite (20 March 2007 Final Office Action ¶ 25);
2. The rejection of claim 22 as being indefinite (20 March 2007 Final Office Action ¶¶ 32(a) and 32(b));
3. The rejection claims 23-25 as being indefinite (20 March 2007 Final Office Action ¶32(c));
4. The rejection of Claim 29 as being indefinite (20 March 2007 Final Office Action ¶ 29));

5. The rejection of claims 30-32 and 36 as being indefinite (20 March 2007 Final Office Action ¶30);
6. The rejection of claim 35 as being indefinite (20 March 2007 Final Office Action ¶31)
7. The rejection of claims 18-31 and 51 under 35 U.S.C. §103(a) (20 March 2007 Final Office Action ¶22) over McMaster (U.S. 6,146,902) in view Andre *et al.* (In: Modern Vaccinology, (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, NY, *pp.* 41-54, (1994)), Levine *et al.* (In: Abstracts of the Tenth International Pathogenic *Neisseria* Conference, (Ed) Zollinger *et al.* Baltimore, MD, *pp.* 228-230 (1997)), and Lindberg (Vaccine, 17:S28-S36 (1999)); and
8. The rejection of claims 18-36, 46, 48-51, 56, and 57 as obvious (20 March 2007 Final Office Action ¶27) over Costantino *et al.*, (Vaccine, 10:691-698 (1992)) and McMaster in view of Andre *et al.*, Levine *et al.*, and Lindberg.

The Examiner objected to the Specification. Additionally, all of the pending claims currently stand rejected as stated below:

1. The amendment to ¶33 of the Specification is objected to under 35 U.S.C. §132 as introducing new subject matter (12 December 2007 Office Action ¶5);
2. Claims 18-36, 46, 48-51, 56 and 57 stand rejected under 35 U.S.C. §112, ¶1, as containing new subject matter (12 December 2007 Office Action ¶15/16);
3. Claims 18-33 are provisionally rejected under the non-statutory doctrine of obviousness type double patenting over co-pending application Ser. No.: 11/232,160 (12 December 2007 Office Action ¶15);
4. Claim 22 stands rejected under 35 U.S.C. §112, ¶2, as being indefinite (12 December 2007 Office Action ¶17(a));
5. Claim 35 stands rejected as being indefinite (12 December 2007 Office Action ¶17(b));
6. Claim 48 stands rejected as being indefinite (12 December 2007 Office Action ¶17(c));
7. Claim 48 stands rejected as being indefinite (12 December 2007 Office Action ¶17(d));
8. Claims 23-25, 36, 49, and 50 stand rejected as being indefinite (12 December 2007 Office Action ¶17(e));
9. Claims 18-36, 46, and 48-51 stand rejected of under 35 U.S.C. §103(a) (12 December 2007 Office Action ¶18) over Costantino *et al.*, in view of McMaster, Chong *et al.*, (WO 99/42130), Lingappa *et al.*, (Vaccine, 19:4566-4575, August 2001), Perkins *et al.*, (J. Amer. Med. Assoc., 283(21):2842-2843, 7 June 2000) and Morley *et al.* (Vaccine, 20:666-687, 12 December 2001);
10. Claims 56 and 57 stand rejected as being obvious (12 December 2007 Office Action ¶19) under Costantino *et al.*, in view of McMaster, Chong *et al.*, Lingappa *et al.*, Perkins *et al.*, Morley *et al.* and Scheerson *et al.* (U.S. 6,632,437).

The amendments and remarks submitted herein are intended to be responsive to the Examiner's concerns, to advance the prosecution of the present application, and to place the application in condition for immediate allowance. Reexamination and reconsideration of the pending claims as amended herein is respectfully requested.

Objection 1: Alleged New Subject Matter in the Specification

The applicant has amended, without prejudice, Specification paragraph [0033] to rewrite the paragraph with its original verbiage. The applicant does not however acquiesce to the Examiner's arguments. Applicant continues to maintain that the amendments to paragraph [0033] submitted in the 7 June 2005 paper are supported by 1) the citation to "Vaccine Design, the Subunit and Adjuvant Approach, 1995 (M. F. Powell and M. J. Newman, eds., Plenum Press, N.Y.)" originally provided in the paragraph as it was filed; 2) the citation contained in Powell and Newman at *p.* 492 (*See*, Powell and Newman, Ch. 20, *pp.* 492) to the H.R. Allcock and S. Kwon reference (Macromolecules, 22:75-79 (1989)); and 3) the applicant's clear and unambiguous provision of proper chemical names for common abbreviations used in the art. The amendments to Specification paragraph [0033] submitted in the applicant's 7 June 2005 paper would not add new matter if introduced again at a later date.

Rejection 2: Alleged New Matter in the Claims

Claim 18 stands rejected as allegedly containing new subject matter. (12 December 2007 Office Action ¶15/16).[1] The Examiner's arguments can be summarized into two themes: 1) opposition to the term "mammal" in claim 18; and 2) opposition to the term "to one or more of said polysaccharides."

Applicant must respectfully disagree with the Examiner's arguments. Specification paragraphs [0078-0091] note the successful administration of combinations of the inventive compositions to "mice, rats and rabbits" (Specification ¶¶ 0078-0081) and to humans (Specification ¶¶ 0082-0091). Likewise, there is ample support in the Specification and the original filed claims for the term "to one or more of said polysaccharides." Nevertheless, without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the

above-noted subject matter, the applicant has amended claim 18. Support for the present amendments to claim 18 can be found throughout the Specification, most notably, and specifically at ¶¶ 0017-0021, 0036, 0037, and 0078-0091.

Applicant respectfully reminds the Examiner that the *In re Rasmussen* decision reversed a decision of the Patent and Trademark Office Board of Appeal ('Board") affirming the examiner's rejection under 35 U.S.C. §112, ¶1, and §132 of the claim at issue as allegedly adding new matter to the specification for not finding *in haec verba* support in the specification. (*In re Max Otto Henri Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (1981)). Chief Judge Markey called the Board's requirement for *in haec verba* support in the specification for every newly added claim term an impermissible "***exaltation of form over substance***." (*Rasmussen, p.* 1215, *n.* 7, emphasis added). He further stated that "***[b]roadening a claim does not add new matter to the disclosure. Disclosure is that which is taught, not that which is claimed***." (*Rasmussen, p.* 1214, emphasis added). Furthermore, MPEP §2163(I)(B) acknowledges that the specification is support for all that it expressly, implicitly, or inherently teaches. The present amendments do not add new matter. Applicant requests withdrawal of this rejection.

Rejection 3: The Provisional Obviousness Type Double Patenting Rejection

Claims 18-33 are provisionally rejected under the non-statutory doctrine of obviousness type double patenting over co-pending application Ser. No.: 11/232,160. (12 December 2007 Office Action ¶15). Applicant respectfully requests that this rejection be held in abeyance until allowable subject matter is indicated in either application. At such time, applicant will either traverse the rejection(s) or establish co-ownership of the respective applications and file a terminal disclaimer mooting the rejection(s).

Rejections 4, 5, 6, 7, and 8: The Indefiniteness Rejections

Claims 22-25, 35, and 48, stand rejected as being indefinite. The indefiniteness rejections are addressed in the order in which they were presented. (12 December 2007 Office Action ¶17(a)-(e)).

[1] Paragraphs 15 and 16 of the 12 December 2007 Office Action appear to inadvertently combine separate and distinct new matter and provisional obviousness type double patenting rejections.

¶17(a) claim 22: Applicant has amended claims 18, 22, and 29 for improved clarity and consistency as suggested by the Examiner.

¶17(b) claim 35: Applicant has amended claim 35 for improved clarity and consistency as suggested by the Examiner.

¶17(c) claim 48: Applicant has amended claim 48 for improved clarity and consistency as suggested by the Examiner.

¶17(d) claim 48: Applicant has further amended claim 48 for improved clarity and consistency as suggested by the Examiner.

¶17(e) claims 23-25, 36, 49, and 50: The above-mentioned amendments to claims 22, 35, and 48 are sufficient to moot the instant rejections over dependent claims 23-25,36, 49, and 50.

Applicant gratefully acknowledges the Examiner's suggestions for overcoming the indefiniteness rejections. Applicant respectfully requests these rejections be withdrawn.

Rejections 9 and 10: The Obviousness Rejections

The Examiner made two obviousness rejections in the 12 December 2007 Office Action. The first rejection was over claims 18-36, 46, and 48-51 as allegedly being obvious over Costantino *et al.*, in view of McMaster, Chong *et al.*, Lingappa *et al.*, Perkins *et al.*, and Morley *et al.* (12 December 2007 Office Action ¶18). The second rejection over claims 56 and 57 is moot in view of the cancellation, without prejudice, of these claims. For the following reasons, the rejection over claims 18-36, 46, and 48-51 is traversed and should be withdrawn.

Applicant would like to clarify several initial matters. First, the Examiner failed to specifically address the objective evidence presented in the last paper in the form of 3rd party references and supporting remarks. The applicant's objective evidence and remarks are thus deemed accepted. The instant obviousness rejection should be withdrawn without further delay or prejudice to the applicant's interests. Despite the Examiner's failure to rebut the applicant's previously submitted evidence and remarks, the applicant will nonetheless provide additional remarks herein expressly to position the case for further actions.

Second, the Examiner states that the "[i]nstant claims are granted the effective filing date of the instant application due to the new matter identified above" and because of this Lingappa *et*

al. and Morley *et al.* are prior art. (¶18). The applicant respectfully submits that the remarks and/or amendments submitted above remove the instant new matter rejection over claim 18.

The instant application was filed on 22 January 2002 and effectively claims priority to U.S. Provisional Application Ser. No.: 60/263,435 filed on 23 January 2001. The instant application's 23 January 2001 priority date precedes the respective, August 2001, and December 2001, reference dates of Lingappa *et al.* and Morley *et al.* The Lingappa *et al.* and Morley *et al.* references therefore are not available as prior art. Applicant discusses the instant rejection as consisting of Costantino *et al.*, in view of McMaster, Chong *et al.*, and Perkins *et al.*

Third, as noted above, the Andre *et al.*, Lindberg, Levine *et al.*, Granoff (WO 98/58670) and Ambrosch *et al.* (Bul. WHO 61(2):317-323 (1983) references have all been removed from the Examiner's rationale put forth as support for the case of *prima facie* obviousness.

The Chong *et al.*, reference is of record. The last rejection over Chong *et al.*, alleging anticipation, was made in the 7 December 2004 Office Action. Remarks in applicant's 7 June 2005 paper overcame this rejection. Chong *et al.* has not previously been used in any obviousness rejection and applicant objects to raising Chon *et al.* at this point in prosecution three years after its last appearance in the prosecution.

Finally, applicant wishes to note for the record his objection to the perpetual revolving selection of references each of which has been well discussed and of record for more than four years in establishing grounds of rejection. These evergreen references which appear to come and go at the Examiner's election. Applicant objects to this piecemeal examination which is specifically prohibited by the MPEP.

The Legal Standard for Obviousness Examinations

The test of obviousness was set forth by the U.S. Supreme Court in the *Graham v. John Deere Co.*, decision. (*Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966)). *Graham* set out four key inquires that must be considered in determining obviousness under §103: 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) weigh any relevant secondary considerations of nonobviousness. All *Graham* factors must be considered

and each piece of the applicant's evidence of nonobviousness going to the factors must be weighed.

The U.S. Supreme Court's recent *KSR v. Teleflex* decision did nothing to undermine or diminish the importance of the landmark *Graham* decision. (*KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (U.S. Apr. 30, 2007)). The *KSR* decision did not strike down the well settled teaching, suggestion, motivation to combine ("TSM") test promulgated by the Federal Circuit. The *Graham* decision in fact emphasized that the TSM is one important component of obviousness examination.[2] What the Court cautioned against were rigid application of the TSM test that failed to account for common sense.

It is important to note that the *KSR* decision was based on facts arising from a simple and predictable mechanical art. The Court found that the level of skill in the pertinent art was that of an undergraduate degree in mechanical engineering or an equivalent level of industry experience (*i.e.*, any working knowledge of simple levers and pivots, and stock sensor components) in the automotive industry. (*KSR, p.* 8) The scope and content of the prior art at issue involved the **combination of known and components functioning in their usual and customary ways**. The U.S. Supreme Court did not pass its *KSR* decision in an unpredictable field where function known elements sometimes **cannot be predicted**.

Nonetheless, even when combining known elements the Supreme Court cautioned that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." (*KSR, p.* 14). Thus, the focus of *KSR* can be summarized by saying common sense dictates that the predictability, and conversely the unpredictability, in a given field of inventive endeavor must be weighed in every obviousness determination.

Graham explicitly cautions (*i.e.*, the lower courts, the Patent Office, and examiners) that standards are needed during examination "to 'guard against slipping into use of hindsight,' and to resist the temptation to read into the prior art the teachings of the invention in issue."

[2] There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. (MPEP § 2143.01). Second, there must be a reasonable expectation of success. (MPEP § 2143.02). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP § 2143.03).

(*Graham, p.* 36) (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (6th Cir. 1964)). As has been stated by others, the TSM provides the guard. The prohibition against the use of hindsight during obviousness examinations is alive and well. The *KSR* decision did not "green-light" the use hindsight during obviousness examination.

Applicant believes the rigid TSM analysis rejected in *KSR* is currently being employed in the instant case because the Examiner has disregarded the totality of evidence pertaining to the *Graham* factors is will be shown below.

Obviousness examination must be undertaken against the scope and content of the prior art at the time of invention. The scope and content of the prior art must be established by objective evidence submitted on the part of both Examiner and the applicant. Applicant believes that his remarks and objective evidence (*i.e.*, 3rd party references showing the scope and content of the art, the differences between the claimed invention and the prior art; and the level of ordinary skill in the prior art at the time of invention) submitted in his last paper were **disregarded** and not given due weight and consideration during the preparation of the instant Office Action. Applicant's belief is based on the **complete absence** of any discussion or rebuttal of the applicant's citations and remarks. This situation appears to exist despite the obviousness examination instructions set forth by the U.S. Supreme Court in *Graham* and recently reiterated in the *KSR* decision. Applicant's attempt to properly portray the uncertainty and unpredictability of the art at the time of invention through this evidence have not been properly considered, and indeed, apparently ignored in the present Office Action.

For instance, in the 3 April 2006 paper, the applicant objectively established the scope and content of the prior art concerning unpredictability in the field of invention by submitting remarks and providing a citation to a 1998 reference by Gizurarson, "*Clinically Relevant Vaccine-Vaccine Interactions; A guide for Practitioners.*" Gizurarson describes unexpected and unpredictable vaccine-vaccine interactions and prominent vaccine failures in a number of vaccine candidates across a wide swath of the vaccinal arts. It was further submitted at the time that the Examiner was trivializing the unpredictability in the field of invention. The Examiner sought to rebut the Gizurarson paper in the next Office Action of 20 March 2007. However, the rebuttal failed to understand the point of unpredictability in the field of invention and the continued apparent trivialization of that unpredictability when the Examiner stated:

> Gizurarson teaches how combining a viral vaccine that is not a conjugate vaccine, i.e., 'attenuated measles vaccine', with an unconjugated group A and C meningococcal 'polysaccharide' vaccine did not affect the meningococcal seroconversion, but only depressed the immunogenicity of the attenuated measles vaccine. Instant claims however are not drawn to an immunological combination compositions wherein two unconjugated meningococcal capsular polysaccharides are mixed with an 'attenuated' viral vaccine.

(20 March 2007 Office Action, *p.* 11, emphasis in original). The applicant is conscious of the current claim elements and also of the particulars of the Gizurarson paper. The applicant did not when he submitted Gizurarson, nor does he now seek, to assert Gizurarson provides a direct teaching away from the instantly claimed compositions. Applicant's remarks were directed to establishing the scope and content of the prior art as it pertained to and influenced the "expectation of success" and alleged "motivation to combine the references" in the unpredictable field of vaccinology in the manner consistent with the proper *Graham* analysis.

Candidate vaccine compositions, even those anticipated to work and which are administered in human clinical trials do sometimes fail. For instance, Nabi Pharmaceutical's candidate conjugate vaccine against *Staphylococcus aureus* failed during late stage Phase III clinical trials. The SmartMoney.com Website reported the following concerning Nabi's failure, "'The results are certainly a tremendous surprise and disappointment for all of us,' said Thomas McLain, Nabi's chief executive . . . 'All indications, including the previous Phase III trial, supported we had a viable product with the potential to prevent a major cause of health-care-associated infections.'" (SmartMoney.com, accessed 2 November 2005 [Appendix 1]; *see also*, Forbes.com, accessed, 2 November 2005 [Appendix 2]; and Forbes.com "Market Scan," accessed, 2 November 2005 [Appendix 3]). The Nabi polysaccharide-protein conjugate *Staphylococcus aureus* vaccine candidate failed to elicit the expected immune responses.

The applicant must respectfully once again request the Examiner to reconsider the remarks from his last paper giving them due consideration and weight on the scope and content of the prior art as required by *Graham* and *KSR*. Applicant respectfully requests that the Examiner specifically address each of the following citations and supporting remarks.

Applicant again discusses the Lindberg paper previously made of record as it pertains to the scope and content of the prior art. The Lindberg paper is devoid of data concerning any glycoconjugate. It does not teach or suggest with the required specificity how to make and use

any composition pertaining to *N. meningitides* serogroups of A, C, Y, and W-135. It should be viewed as a topical review of the field generally. It was published in a special review edition of the subject journal. It does not contain the requisite evidentiary support necessary to serve as a component of a *prima facie* obviousness rejection. The applicant pointed out many of these shortcomings on various occasions already. At best, Lindberg provides generalized hope for the eventual development of a multivalent vaccine against meningococcal disease.

Contrary to the Examiner's previous assertions concerning *N. meningitides* B-serotype polysaccharide-protein conjugates, the Lindberg paper teaches that B-serotype conjugates were an unfulfilled promise. To illustrate, Lindberg devotes an entire section (*i.e.*, § 4.2) to describing the difficulties in making a *N. meningitides* serotype B conjugates. It was well know in the art that the B-serotype polysaccharide is poorly immunogenic in humans due to humans' innate immunological tolerance for the B serotype polysaccharide. This tolerance is due to the structural similarity of the polysaccharide to an embryonic neural cell adhesion molecule. Nevertheless, Dr. Lindberg maintains that there is the promise of an efficacious *N. meningitides* serotype B polysaccharide-protein conjugate. (Lindberg, S34, §4.2, entire paragraph). To date, there remains no widely efficacious B-serotype vaccine, and in particular, no B-serotype polysaccharide-protein conjugates.

Lindberg himself recognizes the unpredictability of the vaccine art. For example, §2.4 of the Lindberg paper describes one genetic basis for vaccine failure. This is an example of art recognized unpredictability in the field of vaccinology. Dr. Lindberg states "Although the use of glycoconjugate vaccines may overcome some of the allotype associations with T-cell independent responses to polysaccharide vaccines, *it may not be the panacea we hoped for.*"[3] (Lindberg, S31, §2.4, ¶ 4, emphasis added). Similarly, §3.2 of the paper speaks of other potential genetic based hurdles to overcome in the production of efficacious polysaccharide-protein conjugate vaccines. These statements cast doubt on the prospects for successfully producing glycoconjugate vaccines.

Furthermore, Dr. Lindberg predicted the development of a "pneumococcal conjugate vaccine [that] will contain from 9 to 11 different polysaccharides." (Lindberg, S32, §3.1, ¶ 5). The Wyeth Pharmaceuticals, Inc., PREVNAR® heptavalent (*i.e.*, 7 serotypes) pneumococcal-

polysaccharide-protein conjugate vaccine remains the only licensed polysaccharide-protein conjugate pneumococcal vaccine.

Dr. Lindberg himself speaks of a SURPRISING and UNEXPECTED failure of *N. meningitides* A and C-serotype polysaccharide-protein conjugates to induce immunological memory (a hallmark of a successful polysaccharide-protein conjugate vaccine). (Lindberg, S34, §4.1, ¶ 4). Dr. Lindberg summarizes the failure described in the 1997 paper by Leach *et al.* (Leach *et al.*, *Induction of immunological memory in Gambian children by vaccination in infancy with a group A plus C meningococcal polysaccharide-protein conjugate vaccine*, J. Infect. Dis., 175:200-204 (1997)). (Appendix 4). Notably, the BIVALENT serotypes A and C conjugates administered concomitantly failed to produce the hoped for results. The Leach *et al.* paper provides further evidence that polysaccharide-protein conjugate vaccines are unpredictable even in cases of as few as two known glycoconjugates being concomitantly administered. This point is particularly relevant the scope and content of the prior art—not only as it relates to the unpredictability in the field of vaccines generally—but to compositions of meningococcal polysaccharide-conjugates. Applicant's remarks concerning Leach *et al.* were not rebutted in the instant Office Action.

As a final example of Dr. Lindberg's hopeful predictions, in §5 of the paper, Dr. Lindberg opines that successful polysaccharide-protein conjugate vaccines will be developed against: 1) group B *streptococci*; 2) *Salmonella typhi* Vi polysaccharide; and the capsular and lipopolysaccharide of 3) *Escherichia coli*; 4) *Shigella sonnei*; and 5) *S. Flexneri*. To the applicant's knowledge, no such efficacious polysaccharide-protein conjugate vaccines exist. This highlights the somewhat hyperbolic nature of the paper and the unpredictability in the field of vaccinology. In view of the forgoing, it is clear as a whole that the Lindberg reference is merely a collection of desires for effective vaccines that have largely eluded those of skill in the art.

The Examiner has stated Levine *et al.* provides a "cost-effectiveness analysis for routine immunization" with a tetravalent A, C, Y and W-135 polysaccharide-protein conjugate vaccine. (20 March 2007 Final Office Action, ¶27). The Examiner has merely substituted Perkins for Levine *et al.*, as providing generalized economic and epidemiological motivation for an A, C, Y,

[3] Mr. Lindberg's word choice is interesting, "*panacea*" is defined in Webster's Ninth New Collegiate dictionary

W-135 glycoconjugate vaccine. Applicant believes his previous comments relating to Levine *et al.* apply equally to Perkins. Briefly, Levine is replete with baseless suppositions regarding the nature of future vaccine modeled therein. The self-described "**key estimates**" mentioned in Levine *et al.* have previously been discussed. (Levine *et al.*, *p.* 228, ¶ 2, emphasis added). Levine *et al.* state "The C-E of MenConj vaccine in this analysis **depends** on some **important assumptions**. First, it must be administered in the same syringe with the Hib conjugate vaccine (or other appropriate vaccine)." (Levine *et al.*, *p.* 229, ¶ 5, emphasis added). Levine *et al.* fail to provide any suggestion of how to achieve this hypothetical vaccine. Similarly, Perkins fails to teach or suggest how to achieve any of the hypothetical vaccine multivalent compositions.

Perkins, like the Levine *et al.* reference before it, provides no probative support in relation to the reasonable expectation of success. The reasonable expectation of success is a reasonable likelihood of TECHNICAL success. It does not come from an economic success, nor from a hoped for medical success in ameliorating world-wide meningococcal disease burdens. As was said before, extending the Examiner's apparent rational for applying Levine *et al.*, and now Perkins one could draft a paper arguing that a cancer vaccine or perhaps an AIDS, or almost any other vaccine for that matter, would certainly be cost-effective and medically beneficial as compared to the wrath of a disease and its costs on society thereby rendering such vaccines obvious. Next, the Examiner could simply pick out the required claim elements from any number or even multitude of references and argue that there was sufficient economic and medical motivation for making the combination and thus a *prima facie* case of obviousness has been established. If this type of examination is allowed, then it is hard to imagine any patentable therapeutic compositions or methods. Applicant has repeatedly argued strongly against the probative value of such generalized cost-benefit analysis papers as valid evidentiary support in obviousness examinations. References such as Levine *et al.* and Perkins should be accorded no evidentiary weight when establishing a *prima facie* case of obviousness as required under *Graham* and *KSR*. Indeed, properly viewed the demonstration of a need and potential market success of such hypothetical vaccines underscores the long felt need and the failure of others to provide the vaccine of the present invention.

(1985) as "a remedy for all ills or difficulties; cureall."

Notably, analogous papers regarding the modeling of the cost-effectiveness of a prostate cancer chemotherapeutic and of an AIDS vaccine indeed exist. (*See, Svatek et al., The cost of prostate cancer chemoprevention: a decision analysis model,* Can. Epidemiol. Biomarkers Prev, 15(8):1485-1489 (2006) [Appendix 5]; and *Bishai et al., Modeling the economic benefits of an AIDS vaccine. Vaccine*, 20:526-531 (2001) [Appendix 6]). Five years after Bishai *et al.*, we remain waiting for the AIDS vaccine Bishai *et al.*, modeled.

In yet another unrebutted example, it was noted that Scott *et al.*, performed a cost-benefit analysis concerning the use of meningococcal vaccines in college freshmen. Scott *et al.* came to the conclusion that it was not cost effective to use meningococcal vaccines despite the disease prevention that would be obtained. (*See*, Scott *et al., Vaccinating First –Year college Students Living in Dormitories for Meningococcal Disease*, Am. J. Prev. Med. 23(2):98-105 (2002) [Appendix 7]). Despite this analysis, the Center for Disease Control, Advisory Committee on Immunization Practices, and the American Academy of Pediatrics as well as most universities have strongly urged the use of the MENACTRA® vaccine in this population. The Scott *et al.* reference teaches away from continuing efforts to develop meningococcal vaccines as are presently claimed. Given the discord in these types of papers, the applicant submits that none of the particular aforementioned references are of any value in actually guiding one skilled in the art in developing the presently claimed therapeutic agents.

In regard to McMaster, the record shows that the Examiner stated "McMaster's disclosure differs from the present invention in not expressly teaching a combination composition of two, three, or four conjugates of the purified capsular polysaccharides of *Neisseria meningitides* of serogroup A, C, Y and W-135 conjugate to a diphtheria toxoid protein." (7 December 2004 Office Action ¶22). Costantino *et al.* is directed solely to bivalent A and C serotype polysaccharide-protein conjugates. Accordingly, the record also rightly further shows that "[t]he conjugate vaccine of Costantino *et al.* differs from the instant invention in not containing W-135 and/or Y capsular polysaccharide conjugate(s) therein." (12 December 2007 Office Action ¶18). Given this admission, the Examiner is respectfully requested to explain the continued relevance of the Costantino *et al.* to the recited combination of references in view of the aforementioned failure of a bivalent combination of A and C polysaccharide-protein conjugates described in Leach *et al.*

The Gizurarson paper was brought to the Examiner's attention to show that vaccinology is often an unpredictable art. The paper shows that even combinations of antigens which might be obvious to try are often not efficacious, only marginally efficacious, and in some instances even produce unexpected deleterious effects. Applicant submits the Gizurarson paper to highlight that one skilled in the art would appreciate that vaccinology is generally unpredictable. This general point was likewise demonstrated in the Lindberg paper also discussed above.

By way of further example of unpredictability, the applicant respectfully submits a 2005 paper by Buttery *et al.*, published in the Journal of the American Medical Association. (Buttery *et al.*, *Immunogenicity and safety of a Combination Pneumococcal-Meningococcal Vaccine in Infants*, 293(14):1751-1757 (2005)). (Appendix 8). Briefly, the Buttery *et al.* paper looked "To determine the safety and immunogenicity of a combination 9-valent pneumococcal-group C meningococcal conjugate vaccine (Pnc9-MenC) administered as part of the routine UK infant immunization schedule." (Buttery *et al.*, *p.* 1751). In particular, Buttery *et al.* determined that the "Pnc9-MenC combination vaccine administered to infants at ages 2, 3, and 4 months **demonstrated reduced** group C meningococcal immunogenicity compared with MenC vaccine. The immunogenicity of concomitantly administered Hib and DTwP vaccines **was also diminished**. . . . [and that] The **reduced** MenC immunogenicity may limit the development of the Pnc9-Menc vaccine." (Buttery *et al.*, *p.* 1751, emphasis added).

In commenting on their research, Buttery *et al.* state "It illustrates the **unpredictability** of immunogenicity when **combining multivalent vaccines, each immunogenic in separate form**. (Buttery *et al.*, *p.* 1754, emphasis added).

Additional references can be made available for the Examiner's considerations that speak to the unpredictability in the field of vaccine development.

All of the above (and previously made) remarks notwithstanding, and while in no acquiescing to the Examiner's arguments or conclusion that a *prima facie* case of obviousness has been established, the applicant would like to again provide the following additional remarks that directly put Secondary Considerations of non-obviousness in front of the Examiner. Secondary Considerations of non-obviousness MUST be considered according to the U.S. Supreme Court when an examiner is determining the alleged obviousness of an applicant's claims. (*Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966)). The Federal Circuit

has followed this mandate from its creation. For instance, the *Custom Accessories, Inc.*, decision held "[u]nder *Graham*, objective evidence of nonobviousness includes commercial success, longfelt but unresolved need, failure of others, and copying. When present, such objective evidence must be considered." (*Custom Accessories, Inc., v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 1 USPQ2d 1196 (Fed. Cir. 1986); accord, *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983) (holding, secondary considerations must be given due weight by the examiner and Board of Appeals during *ex parte* prosecution); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983) (holding, "So-called 'secondary' considerations, such as long-felt need, commercial success, and initial expressions of disbelief by experts, should be considered in every case for whatever probative value and are not limited to cases where patentability is a 'close' question")).

Notably, the instant Office Action was **completely silent** on weighing the applicant's objective evidence of Secondary Considerations negating and/or overcoming the establishment of a *prima facie* case of obviousness.

First, the Advisory Committee on Immunization Practices (ACIP) recently, June 2007, revised an earlier recommendation so that now **all** 11-18 year olds in the U.S. should given at least one dose "at the earliest opportunity" of the applicant's licensed tetravalent (A, C, Y, and W-135) meningococcal polysaccharide-diphtheria toxoid conjugate vaccine composition known in the medical community as the MENACTRA® vaccine. (MMWR. 56(31):794-795 (2007) [Appendix 10]). The revised recommendation replaced an early less encompassing ACIP recommendation. ACIP is widely known in the medical community as an influential group of 15 experts who provide advice and guidance to the CDC on the most effective means to prevent vaccine-preventable diseases.

The MENACTRA® vaccine has been licensed in the U.S. since 14 January 2005 for administration to those aged 11-55. On 19 October 2007 the MENACTRA® vaccine received further F.D.A. marketing approval for administration in 2-10 year olds. The applicant has enjoyed strong and increasing **commercial success** with their MENACTRA® vaccine product since its licensure. The MENACTRA® vaccine is the only tetravalent (A, C, Y, and W-135) meningococcal polysaccharide-protein conjugate vaccine licensed by the U.S. Food and Drug Administration (F.D.A.) in the U.S. The vaccine has also been licensed in Europe by the

E.M.E.A. Shortly after its U.S. launch, the MENACTRA® vaccine posted 2006 First Quarter sales in the U.S. alone of 53,000,000 € (*See*, Appendix 10, *p.* 2). By the end of December 2007 nearly 15,000,000 doses of the MENACTRA® vaccine had been distributed. Moreover, 2007 saw a 73% increase in the number of dose distributed over the preceding year. The MENACTRA® vaccine product has clearly meet with vast commercial success. "Commercial success is . . . a strong factor favoring nonobviousness." (*Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, USPQ2d 1241 (Fed. Cir. 1986) cert. denied, 477 U.S. 905 (1986)). As a touchstone on the level and value of relevant commercial success, the Federal Circuit held in *Symbol Technologies* that the patentee's products "have enjoyed tremendous commercial success, with about 200,000 devices sold for over 150,000,000 as of the time of trial." (*Symbol Technologies, Inc., v. Opticon, Inc.*, 935 F.2d 1569, 19 USPQ2d 1241 (Fed. Cir. 1991)). The MENACTRA® vaccine has sold roughly 75 times as well as the product noted in the *Symbol Technologies* decision.

Invasive meningococcal disease was recognized as an important public health problem at the time of invention as an illustration, the number of cases of meningococcal disease in the U.S. for all age groups from 1987 through 2001 runs from an approximate high of 3,000 cases in 1987 to an approximately low of 2,250 cases in 2001. The peak number of cases during this time period was approximately 3,500 in 1997. (*See*, MMWR. 2004, 51(53):1-84; MMWR, 1997, 45(53):1-87; CDC, National Vital Statistics Reports, 2003, 52:1-137; and CDC, Active Bacterial Core Surveillance (ABCs) Report, *Neisseria meningitides*, 1997-2005; available at: www.cdc.gov/ncidod/dbmd/abcs). More particularly, meningococcal disease is a serious, rapidly progressive infection that leaves little time for diagnosis and treatment. (*See*, Granoff DM, *et al.* In: Plotkin SA, ed. Vaccines. 4th ed. Philadelphia: W.B. Saunders Co., (2004) [Appendix 11];; Rosenstein NE, *et al.*, New. Eng. J. of Med., 344:1378 (2001) [Appendix 12]; Schuchat A, *et al.*, New. Eng. J. of Med., 337:970 (1997) [Appendix 13]; and Whitney CG, *et al.*, New. Eng. J. of Med., 348:1737 (2003) [Appendix 14]). Early meningococcal disease can present with symptoms similar to common viral illness, making diagnosis difficult. (Id.). *Meningitides* is now the most prevalent etiologic agent of bacterial meningitis among children and adolescents 2 to 18 years of age in the U.S. (*Id.*).

Furthermore, the consequences of contracting meningococcal disease are dire. From 1986 through 2005 approximately 8-12% of all patients who contracted meningococcal disease died demonstrating the severity of the disease. Morbidity in those contracting meningococcal disease was also unfortunately high. Kaplan *et al.*, reported significant morbidity among 159 reported cases of invasive meningococcal disease in patients 19 years old and younger at 10 U.S. children's hospitals from 1 January 2001 to 15 March 2005. Importantly, Kaplan *et al.* report a significant fraction of the reported cases in this age group required serious interventional measures during treatment (*i.e.*, mechanical ventilation: 26%; and administration of vasopressors: 33%). A significant fraction of cases were also associated with severe neurological and non-neurological sequelae, including amputation, skin necrosis, skin graft, post-admission seizures, deafness, ataxia, and hemiplegia (number of cases per sequelae: amputations (2); skin necrosis (14); skin grafts (4); post-admission seizures (9); deafness (14); ataxia (4); and hemiplegia (3)). (Kaplan SL, *et al.*, *"Multicenter surveillance of invasive meningococcal infections in children,"* Pediatrics, 118:e979-e984 (2006)) (Appendix 15).

Serotype distribution of meningococcal disease in the U.S. from 1997-2003 was as follows: serotype B = 34%; C = 24%; Y = 28%; and W-135 (plus minor contributing serotypes) = 14 %. Serotype distribution in Europe from 1998-2002 shows serotypes Y and W-135 accounted for nearly 5% of reported cases of invasive meningococcal disease. Thus, in the years prior to the present invention the vaccinal art and the medical communities recognized that 43% of meningococcal disease in the U.S. was being caused by serotypes Y and W-135 serotype. And even though serotypes Y and W-135 were not as prevalent in Europe (approx. 5% of reported cases) they still accounted for significant disease burden. The above-mentioned figures do not even take into account the morbidity and mortality in places with endemic meningococcal disease such as Sub-Saharan Africa the "*Meningitis Belt.*" Clearly, meningococcal disease caused by serotypes Y and W-135 presented a significant global health burden for many years prior to the present invention.

A 1981 paper by Jennings H.J. and Lugowski C. describes the "successful coupling of the meningococcal groups A, B, and C polysaccharides to tetanus toxoid to yield water soluble conjugates." (Jennings and Lugowski, J. Immunol., 127(3):1011-1018, (Sep. 1981)) (Appendix 16). Despite the early work done on the development of A and C serotype polysaccharide-

protein conjugates, no successful serotype Y and W-135 polysaccharide-protein conjugates were available until the present invention even though meningococcal serotypes Y and W-135 were known to be causing significant morbidity and mortality. Applicant thus respectfully submits that the present invention **satisfied a long felt** but unmet need in the vaccinal art and medical community for successful immunogenic compositions of tetravalent meningococcal serotype Y, W-135, A, and C polysaccharide-conjugates. The success of the MENACTRA® vaccine in the U.S., and world markets, underscores the satisfaction of the **long felt need** for the important compositions presently recited and claimed herein.

While in no way does the applicant concede that a *prima facie* case of obviousness has been established, the Secondary Consideration evidence presented related to the MENACTRA® vaccine when viewed under the framework set forth by the U.S. Supreme Court in the landmark *Graham v. John Deere Co.*, decision strongly points to the non-obviousness of the presently invention.

In view of the remarks previously made of record and those presented herein, the applicant must respectfully submit that the Examiner has not established the *prima facie* obviousness of the pending claims. The pending obviousness rejections should be withdrawn without further delay or prejudice to the applicant's interests.

Respectfully submitted,

Date: 11 JUNE 2008 By: _____

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